Journal of Surgical Oncology 1998;69:45–50

Fluorodeoxyuridine Causes Bilomas After Hepatic Cryotherapy

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Background and Objectives: Hepatic cryotherapy is a method of in situ cytodestruction used for unresectable liver tumours that can be combined with regional cytotoxic administration. We have used intra-arterial chemotherapy with 5-fluorouracil (5-FU) after hepatic cryotherapy but changed to 5-fluorodeoxyuridine (FUDR) because of the arterial toxicity of 5-FU. A new complication was seen.

Methods: A retrospective case note study was performed of 130 patients who had undergone hepatic cryotherapy followed by regional chemotherapy at our centre. Seven patients received FUDR; 123 received 5-FU.

Results: Biloma at the cryotherapy sites was seen in three patients in the FUDR group; two other patients in this group had other types of hepatic collection. Our previous experience with intra-arterial 5-FU in 123 patients after hepatic cryotherapy showed no evidence of this syndrome.

Conclusions: Intra-arterial FUDR should not be used after hepatic cryotherapy, at least during the immediate postoperative period.

J. Surg. Oncol. 1998;69:45–50.

KEY WORDS: **hepatic cryotherapy; intra-arterial chemotherapy; biloma; 5-fluorouracil (5-FU); 5-fluorodeoxyuridine (FUDR)**

INTRODUCTION

Regional arterial therapy has been widely used in the treatment of hepatic metastases from colorectal cancer, with considerably higher response rates than are achieved with systemic chemotherapy [1] and proven survival advantage in two controlled trials [2,3]. The use of adjuvant regional chemotherapy after resection has been shown to increase time to hepatic recurrence significantly [4,5], although no adequately powered studies have yet addressed its effect on survival. We and others have used hepatic cryotherapy to treat unresectable liver metastases [6,7] and have used regional 5-fluorouracil (5-FU) in these patients [8,9]. Because of the incidence of arteritis and low port patency rates, we have more recently used 5-fluorodeoxyuridine (FUDR) via Infusaid pumps. This paper is the first report of a pronounced complication of FUDR treatment after hepatic cryotherapy.

MATERIALS AND METHODS

The charts of all 36 patients in whom Infusaid pumps were inserted by our unit (Department of Surgery, St. George Hospital, University of New South Wales), until September 1996, were reviewed. Of these, eight had other synchronous procedures; the details of the seven patients who had undergone cryotherapy are given in Table I. Serum biochemistry was reviewed and the alkaline phosphatase plotted (Fig. 1). The charts of 123 patients who had received intra-arterial 5-FU using a port and external pump after cryotherapy were also reviewed.

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Accepted 20 June 1998

TABLE I. Intra-Arterial Fluorodeoxyuridine Following Hepatic Cryotherapy

Patient	Operation	Complication	Outcome
1	17.2.96 Right hemi-hepatectomy edge cryotherapy	Nil	
2	29.3.96 Right hemi-hepatectomy edge cryotherapy Cryotherapy lesion segment: III	28.5.96 Necrotic area liver Staphylococcus infection. Massive arterial bleed	Well, following revision
3	27.4.96 Cryotherapy segments: II, III, VII, and VIII	Subcapsular haematoma	Percutaneous drainage
4	18.6.96 Cryotherapy segments: III and V	Biloma Segment. V	Percutaneous drainage
5	18.6.96 Cryotherapy segments: V and VII Aspiration cyst segments: II	3 large biloma	Roux Y cyst jejunostomy
6	25.6.96 Liver resection segment: III Cryotherapy segments: I, V, and VI	Biloma with cystic change in all lesions	No intervention required
7	24.9.96 Cryotherapy segment: VII (atrophic left liver)	Nil to date	

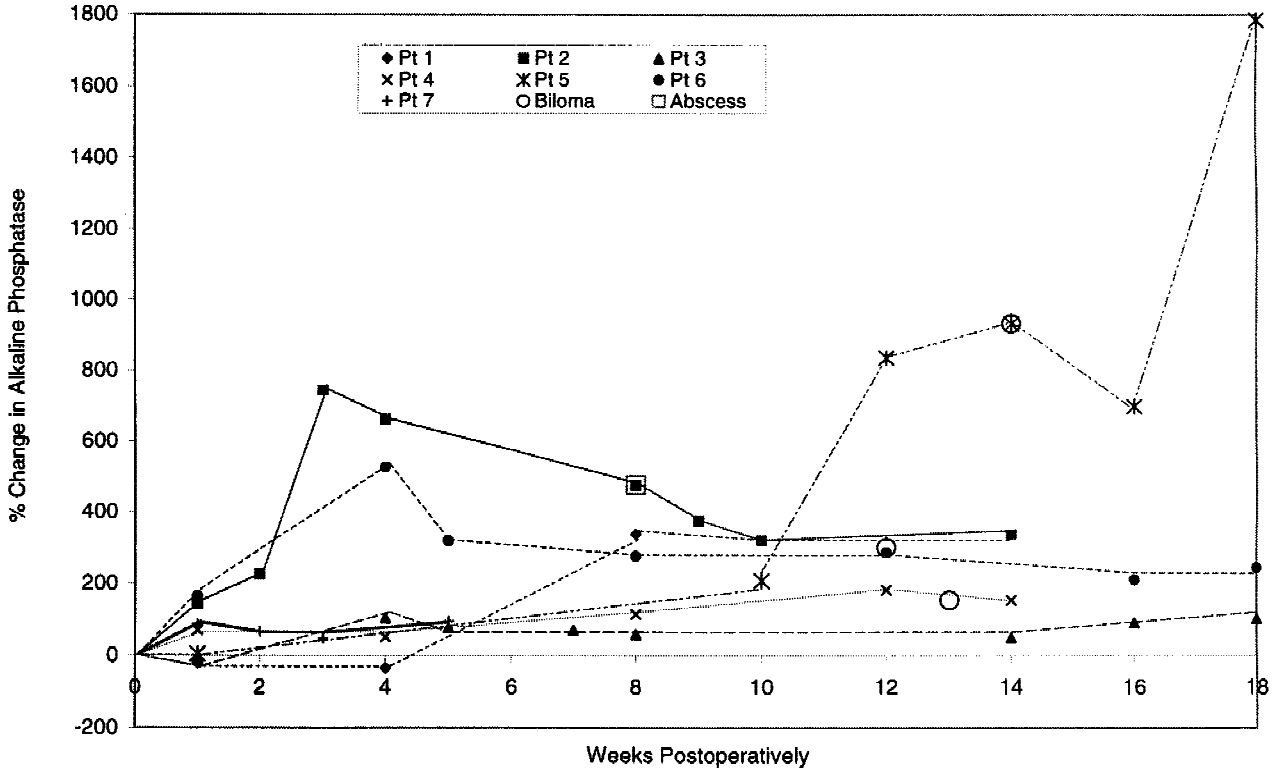

Fig. 1. Serial percentage postoperative change in alkaline phosphatase in seven patients.

RESULTS

Seven patients underwent synchronous hepatic cryotherapy and Infusaid pump implant; of these, one had resection edge cryotherapy alone and experienced no complications. Of the remaining six patients, five developed intrahepatic collections. The site and size of the lesions and the subsequent collections are recorded in Table I. Four contained bile, one was a subcapsular lesion which produced mainly blood on drainage. although this may have been procedural. Computed tomography (CT) scans of patients 5 and 6 are shown in Figures 2–5.

Fig. 2. Patient 6, showing three discrete biloma sites.

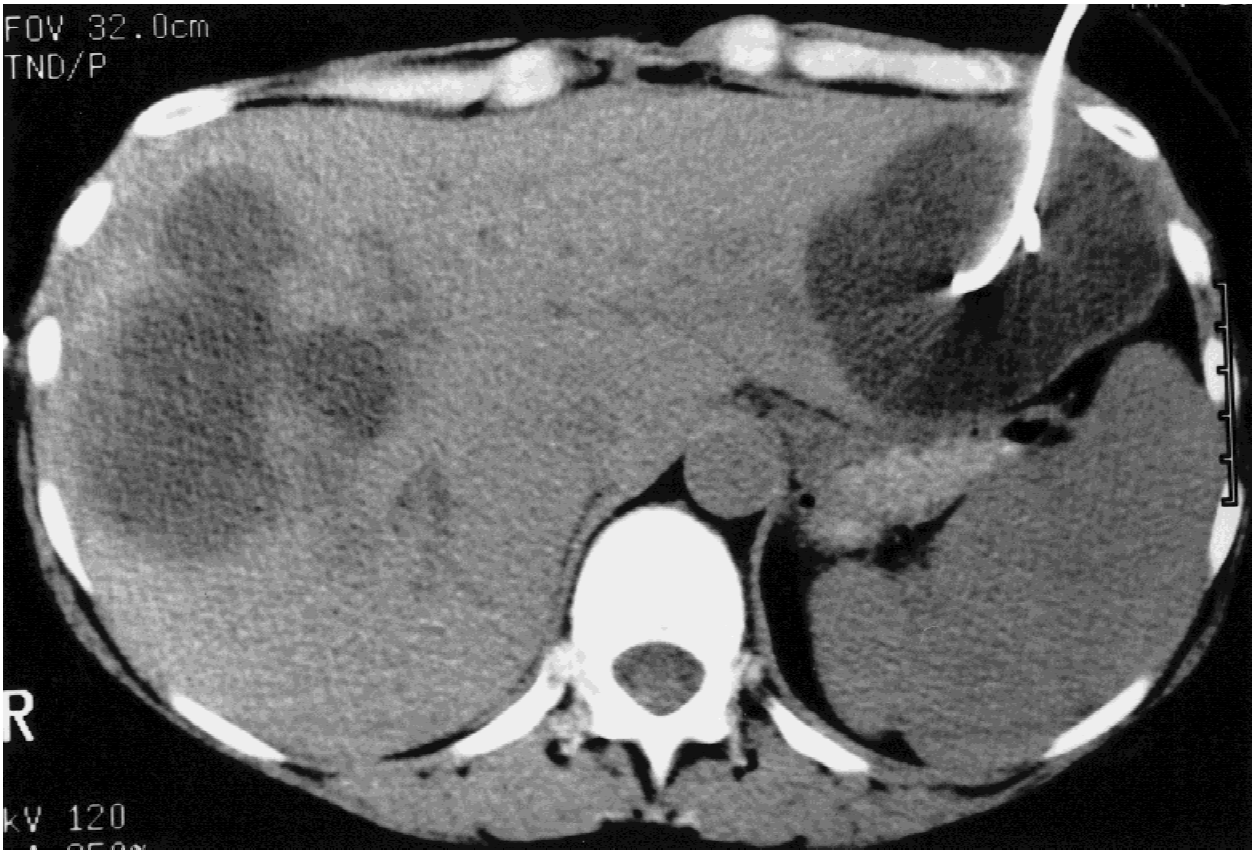

Fig. 3. Patient 5, showing percutaneous drain placed in large biloma of left lateral segment, complex biloma cavity in right lobe visible.

Fig. 4. Patient 5, cholangiogram via drain into left-sided biloma, showing communication with biliary tree and narrowing of ducts at hilus, suggesting scelerosing cholangitis.

Patient 5, who had the largest biloma, underwent percutaneous drainage (Fig. 3); a cholangiogram via the drain in the left-sided biloma (Fig. 4) demonstrated obvious hilar strictures, presumably related to FUDR. Biliary enteric anastamoses were done because of prolonged biliary drainage with resolution of biloma (Fig. 5).

Serial changes in alkaline phosphatase expressed as a percentage of pretreatment value are plotted in Figure 1. Of the three patients who developed obvious biloma, the percentage rise in alkaline phosphatase was 182%, 526%, and 1785%. The biloma occurred at 8−14 weeks after operation.

The biloma was always initially treated by percutaneous drainage, which produced resolution in two cases; one patient continued to drain, and another developed bleeding. The patient with the largest biloma has definite evidence of sclerosis of the bile ducts (Fig. 3). This patient was managed by anastomosing a Roux Y loop onto the three large bilomas, which contained considerable debris; *Staphylococcus albus* and *Xanthomonas* were cultured. Patient 2 also had proven *Staphylococcus aureus* and *Escherichium faecalis* infection in the cavity, and a secondary hemorrhage requiring surgery occurred at 2 months. The hepatic artery catheter was removed and the bleeding controlled by suture ligation of the side hole in the hepatic artery. No bilomas were seen in the 5-FU-treated patients.

DISCUSSION

Biliary toxicity from hepatic artery FUDR treatment is a well-described serious dose-dependent complication, which frequently requires treatment withdrawal [10,11]. In some series, therapy was stopped in more than one-half of the patients because of biliary toxicity. With careful management, biliary stricture and jaundice can usually be avoided. Up to 71% of patients have been recorded to have liver enzyme abnormality with treatment [11].

It has been postulated that biloma may result from biliary manipulation during cryotherapy [12]. This did not become a focus in our study, as we have observed a very high frequency of bilomas in the liver after the use of intra-arterial FUDR after hepatic cryotherapy; this is in marked contrast to our much larger experience with the use of intra-arterial 5-FU after cryotherapy, where this complication was not seen, although we have experience of arterial complications of 5-FU [13]. This complication of FUDR after cryotherapy has not been previously described [14]. We hypothesise that raised biliary

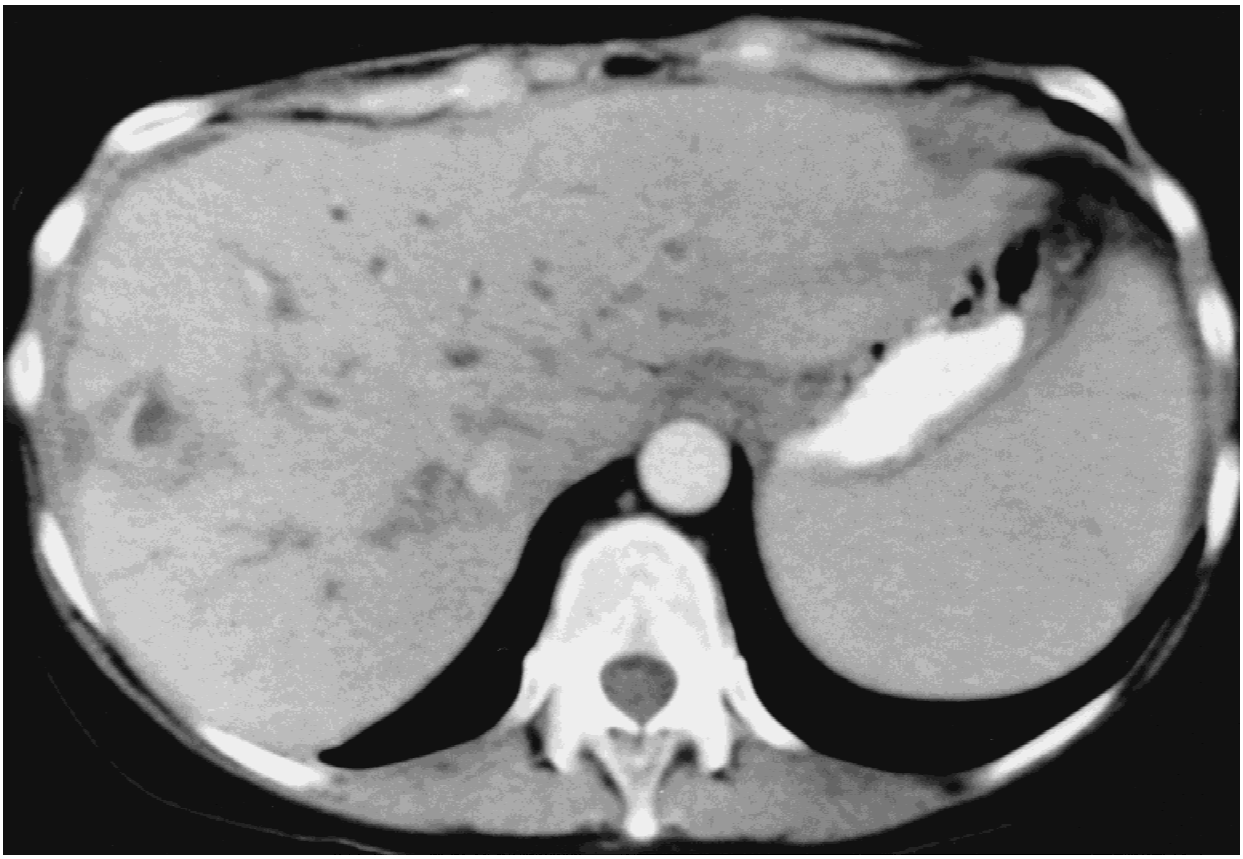

Fig. 5. Patient 5 after multiple biloma-enteric anastamoses.

pressure caused by the onset of sclerosing cholangitis from FUDR results in leakage of bile into the necrotic areas of liver after cryotherapy. We have previously reported the pathological appearance of liver after hepatic cryotherapy in sheep[15], and a firm and eventually fibrous lesion is seen; the radiology of resolving cryolesions treated with 5-FU has also been described and does not include biloma [16]. Whereas FUDR has some advantage over 5-FU in avoiding arterial injury, we would caution against its use after cryotherapy. The arterial bleed, which occurred in patient 2, we believe, was secondary hemorrhage due to infection of the hepatic artery catheter site from the infected biloma and was probably unrelated to the FUDR-cryotherapy-biloma syndrome. Although we have managed two patients just by drainage of their bilomas, this was in peripheral lesions and we would not advocate simple drainage for lesions close to the hepatic artery catheter. Avoidance of drainage is probably advisable, if possible, but was necessary in most of our patients due to pain. The persistent bile drainage in patient 5 was clearly attributable to distal biliary obstruction from FUDR-induced cholangitis. We decided that biliary enteric drainage was most appropriate because of the large cavities with much debris and the rather daunting alternate prospect of multiple stent placements to achieve internal drainage. Regional chemotherapy after hepatic cryotherapy may be of value in reducing or delaying hepatic recurrence, but we would recommend using 5-FU rather than FUDR.

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